

Myocardial ischemia and viability

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1 Introduction

This paper addresses the question of whether and how MCG tests that assess ischemia or viability of the myocardium can add to the diagnostic information gained from standard procedures in asymptomatic and symptomatic patients. We review the diagnostic performance of the exercise electrocardiogram (ECG), the exercise and pharmacological (stress) echocardiogram, the exercise and pharmacological myocardial perfusion imaging, and the positron emission tomography (PET).

2 Myocardial ischemia

Diagnostic tests should be used if the diagnosis of myocardial ischemia is uncertain. Dyspnea on exertion, resting ECG abnormalities, or multiple risk factors for atherosclerosis suggest the possibility of coronary artery disease (CAD). The most predictive clinical finding is a history of chest pain or discomfort.

Although the coronary angiogram has obvious limitations, angiographic lesions remain the clinical gold standard. However, CAD that has not resulted in sufficient luminal occlusion to cause ischemia during stress can still lead to ischemic events through spasm, plaque rupture, and thrombosis.

As with all diagnostic studies, the predictive value of diagnostic procedures is dependent on the prevalence of disease in the population tested. When used in a population with a low prevalence of CAD, such as in cardiovascular screening, these tests are expected to have low positive predictive value, and the majority of positive test results represent false-positive responses. Typical angina makes the pretest probability of disease so high that the test result does not dramatically change probability. Diagnostic testing is most valuable in patients with an intermediate pretest probability. Atypical angina in a 50-year-old man or a 60-year-old woman is associated with about a 50% probability for CAD. Diagnostic testing is most valuable in this intermediate pretest probability category.

2.1 Exercise ECG testing

Meta-analyses demonstrated a wide variability in sensitivity and specificity of the exercise electrocardiogram (1,2). The sensitivity is higher in patients with three-vessel disease and lower in patients with one-vessel disease. The approximate sensitivity and specificity of 1 mm of horizontal or downward ST depression in patients with chest pain typically seen by the family practitioner are 50% and 90%, respectively (3,4). The diagnostic value of the exercise ECG lies in its relatively high specificity. The sensitivity of the exercise ECG is generally less than the sensitivity of imaging procedures. Baseline ECG abnormalities such as preexcitation, ventricular pacing, greater than 1 mm of ST depression at rest, and complete left bundle branch block greatly affect the diagnostic performance of the exercise test.

2.2 Exercise and pharmacological stress echocardiography

Stress echocardiography is based on the premise that myocardial ischemia causes left ventricular dyssynergy. Either exercise (treadmill or bicycle) or dobutamine is used as the stress modality. In patients with a significant clinical suspicion of CAD, stress echocardiography is appropriate when standard exercise testing is likely to be non-diagnostic, i.e. in the presence of resting ST-T wave abnormalities, left bundle branch block, ventricular paced rhythms, LV hypertrophy, or digitalis treatment. The mean sensitivity is 81% (67% in single vessel disease, 88% in multivessel disease), and the mean specificity is 85% (5).

2.3 Exercise and pharmacological myocardial perfusion imaging

The development of perfusion defects with exercise or pharmacological stress is dependent on abnormal coronary vasodilator reserve; thus, myocardial perfusion imaging is potentially useful for detecting patients who have flow-limiting coronary artery stenosis. After intravenous administration, thallium-201 distributes in proportion to regional blood flow. Therefore, images of the heart shortly after thallium administration show deficits in regions where blood

flow is relatively reduced. The shorter half-life of technetium-99m sestamibi compared with thallium-201 allows administration of a larger dose, with resulting improved count statistics. The average sensitivity and specificity of qualitative exercise thallium-201 SPECT are 89% and 76%, respectively (6,7,8).

3 Myocardial viability

In a large subset of patients with CAD, left ventricular performance is reduced on the basis of regionally ischemic or hibernating or stunned myocardium rather than irreversibly infarcted myocardium. The detection of reversibly dysfunctional myocardium is clinically relevant because left ventricular function in such patients will improve after revascularization.

Stunning is the post-ischemic condition in which there has been full reperfusion, but mechanical recovery is delayed. In animal experiments, stunning can extend over minutes, hours, days or even weeks. In patients, for example after thrombolytic reperfusion, stunning may last for weeks or months. Hibernation means ischemic non-infarcted but dysfunctional myocardium that could "sleep" for weeks or even months, to "wake up" in response to revascularization. Thus, intervention to improve mechanical function is an option for patients with poor left ventricular function.

3.1 Stress echocardiography

Reperfusion-salvaged, stunned (but not functioning at rest) myocardium can respond to inotropic stimulation by pharmacological stress echocardiography. Wall segments that show hypokinesia or akinesia at rest but improved function during low-dose dobutamine infusion often recover function, suggesting that these segments are "stunned". However, when segments show no improvement during dobutamine infusion, functional recovery is less common, suggesting that most of these segments are infarcted.

Segments with initial improvement during low-dose dobutamine infusion but deterioration of function with higher doses frequently are supplied by arteries with significant residual stenoses. Continuing augmentation of systolic wall thickening with higher doses of dobutamine denotes preserved viability and implies the lack of critical stenosis in the infarct-related artery.

The sensitivity and specificity for the detection of stunning myocardium early after myocardial infarction are 95% and 81%, respectively, and the sensitivity and specificity for the detection of

chronic ischemic dysfunction due to hibernation are 85 and 86%, respectively (5).

3.2 SPECT imaging

The retention of thallium-201 is an active process that is a function of cell viability and cell membrane integrity. The ability of the myocardium to retain thallium is a marker of myocardial viability. Over time, "redistribution" of isotope generally occurs in previously ischemic zones, that is, defects related to ischemic myocardium normalize or "fill in."

Late redistribution imaging (24 to 72 hours) and reinjection studies reported excellent positive (83%) and negative (90%) predictive accuracy for improvement in regional ventricular function after revascularization (9).

Comparative studies show that technetium mibi SPECT or thallium-201 SPECT imaging is inferior to FDG PET in assessing myocardial viability.

3.3 PET imaging

Positron emission tomography (PET) with the radiolabelled glucose analogue 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) is an accepted method for the assessment of regional myocardial glucose metabolism, being performed with the aim of evaluating myocardial viability and distinguishing between viable and scar tissue. Comparative analysis of myocardial metabolism and blood flow allows the prediction of potential recovery of wall motion abnormalities after revascularization.

Preserved metabolic activity in myocardial regions with reduced blood flow has been shown to be an accurate clinical marker which can distinguish viable myocardium from myocardial fibrosis, with positive and negative predictive accuracies in the range of 85% in identifying regions that will manifest improved function after revascularization (10). Some studies also suggest that the extent of myocardial mismatch may predict the magnitude of improvement in left ventricular function after revascularization (11,12). However, FDG PET may have some limitations in assessing viability in patients with abnormal glucose metabolism.

4 MCG in ischemia and viability

MCG is a very fast, non-invasive diagnostic procedure. Multi-sensor devices spatiotemporally record the magnetic field at multiple sensor positions which are exactly defined by the geometry of the sensor array. There is no need for a reference lead which facilitates DC recordings, and the future application of vector sensors will enable the

discrimination of the different components of the magnetic field.

Reviewing the literature, there is a very limited number of studies which applied MCG to the fields of ischemia and viability. At the current stage of research it seems impossible to judge about the diagnostic utility of the method. Therefore, this section reviews the first results and indicates the future prospects of the MCG method in diagnosing ischemia and viability.

4.1 ST-T segment analysis

There is strong evidence that the MCG contains information in addition to that which in the ECG can be resolved. The vortex component of the current density distribution generates a magnetic field without any accompanying surface electric potentials. The sensitivity of the MCG to these vortex currents has been demonstrated by measuring ST-T segment shifts in healthy subjects (13,14,15). Systematic research has to be done in patients to investigate the diagnostic impact of this finding. The susceptibility of the inner (subendocardial) layer of the left ventricle to ischemia and its vicinity to the highly conductive blood masses gives rise to the assumption that the detection of vortex currents is of special importance.

Although an abnormal ST-T segment suggests the presence of an abnormal cardiac state, it is recorded with relative frequency in the absence of any disorder. Attempts to identify the etiology of an abnormal ST-segment, T wave, or ST-T segment often fail. The clinical ECG does not differentiate between systolic and diastolic currents of injury. Because in ischemia the diastolic current of injury predominates while the systolic current plays a lesser role (16), DC recordings can differentiate ischemia induced ST-T abnormalities from intraventricular conduction defects, premature ventricular excitation, and repolarization abnormalities caused by left ventricular hypertrophy or glycosides. The feasibility of DC MCG recordings of diastolic currents of injury has been demonstrated (17,18). However, unless the onset of the injury is recorded, even a DC-coupled MCG would not identify the mechanisms of the ST-segment shift. The recording of such long-lasting DC shifts is a great challenge for the developers of DC shielding equipment. It is important to notice that moving ferromagnetic implants (dentures, pacemakers, cardioverter defibrillators, stents, sternal cerclages) may cause considerable artifacts during stress recordings.

The standard electrocardiogram samples the body surface potential only at a limited number of sites. Superior information is expected from multi-lead MCG devices. For example, the body surface potential maps from patients with CAD and normal ECG separated from maps of normal subjects with a sensitivity and specificity greater than 94% (19).

Studies which systematically compare the performance of the exercise ECG and MCG in a representative number of patients with suspected CAD still have to be performed. This has to be done according to the standards in diagnostic test research (20).

4.2 Magnetic source imaging

The goal of magnetic source imaging is to provide detailed spatial and temporal information on the three-dimensional electric activity of the heart.

Because the magnetic field outside the body is determined by the electric activity in the entire heart, it is limited in its ability to resolve the three-dimensional excitation process. Although we can nowadays include several a priori information about the sources, still a lot of source details are not yet included in the models. These are in particular the cellular changes caused by compensatory myocardial hypertrophy and remodeling, the individual architecture of the myocardial fibres, and the amount of scarring in the myocardial walls surrounding the infarcted areas.

Inverse solutions applied to MCG data may be particularly useful in determining the functional impact of single or multiple stenoses before percutaneous transluminal coronary angioplasty by localizing the ischemia currents. This is especially important when coronary angioplasty is targeted to the "culprit lesion," that is, the ischemia-provoking stenosis. Because infarcted tissue is electrically silent, three-dimensional images of the electrical activity of the heart are expected to separate viable myocardium from scars.

Several methods have been tested so far which localize infarcted (21), arrhythmogenic (22,23), and ischemic (24,25) myocardium. The results from larger patient series are expected in the near future.

5 Conclusion

The few data available about MCG in ischemia and viability indicate that the method may have a great diagnostic potential. The drawbacks of the MCG method are the limited availability, the high costs, and the absence of larger clinical studies. Thus, multicenter clinical studies have to be performed in the near future to establish the MCG by defining its sensitivity and specificity. A sensitivity and

specificity of about 80% would result in real clinical application.

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